Armed Forces College of Medicine

AFCM

Physiology of Endocrine Pancreas (1)

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INTENDED LEARNING OBJECTIVES (ILO)

By the end of this lecture the student will be able to:

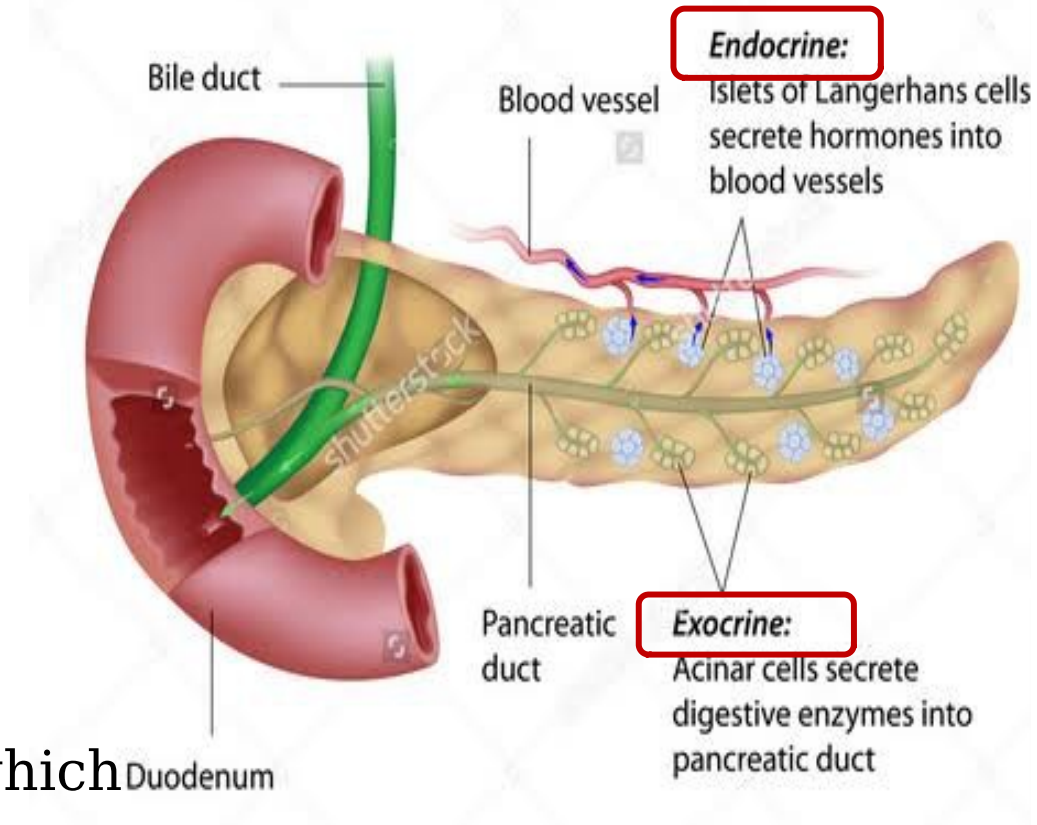
1. Explain the physiological functions of insulin
2. Illustrate how insulin is released from β cells of pancreas in well fed state .
3. Describe insulin receptors, the way they mediate insulin action, and the way they are regulated.
4. Mention the types & functions of glucose transporters found in the body.
5. List the factors that affect insulin secretion.

Endocrine Pancreas

Pancreas is a glandular structure with both endocrine and exocrine functions (mixed gland).

✓ The exocrine part:

- Composed of **acinar cells** which makes the majority of the pancreatic mass.
- They secrete **enzymes** to digest carbohydrates (amylase), proteins (trypsin) & fat (lipase) into the pancreatic duct.



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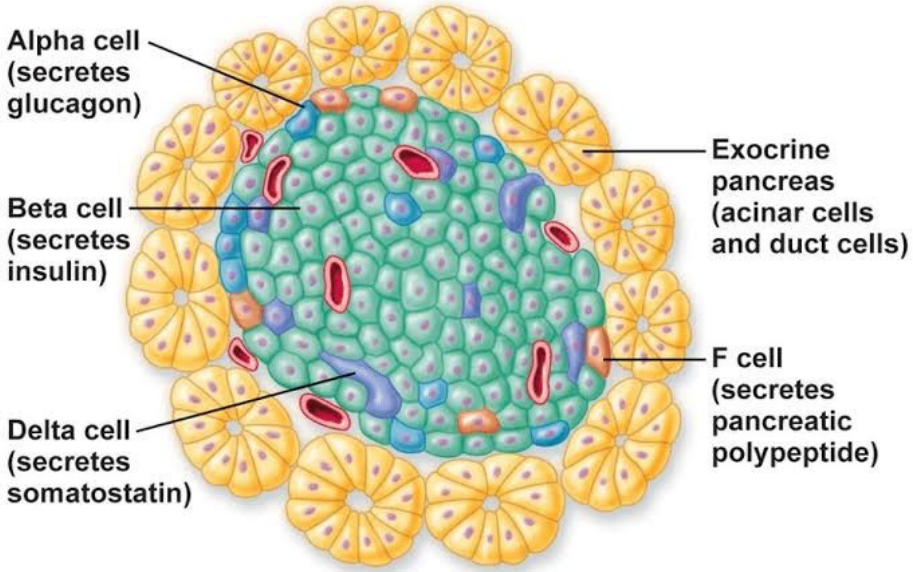
✓ The endocrine part:

- Composed of **pancreatic islets of Langerhans** which represents 1% of the pancreatic mass (1-2 million islets).

What are the hormones secreted by Pancreas?

Islets of Langerhans consists of 4 types of cells which secrete hormones directly into the blood.



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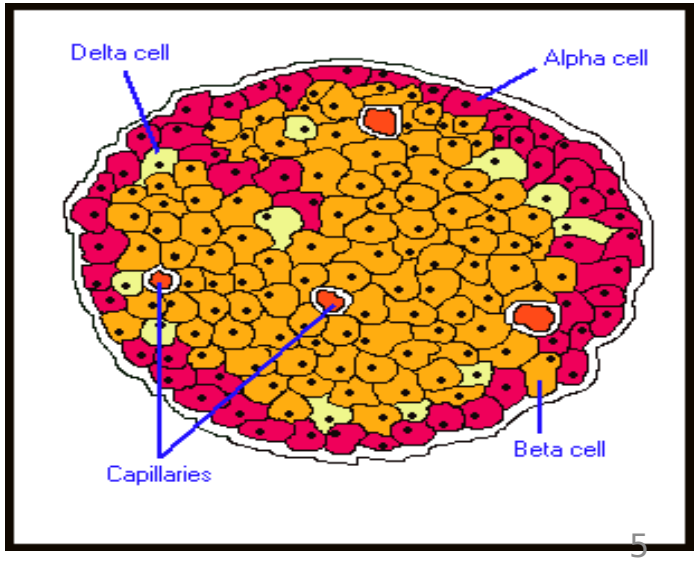
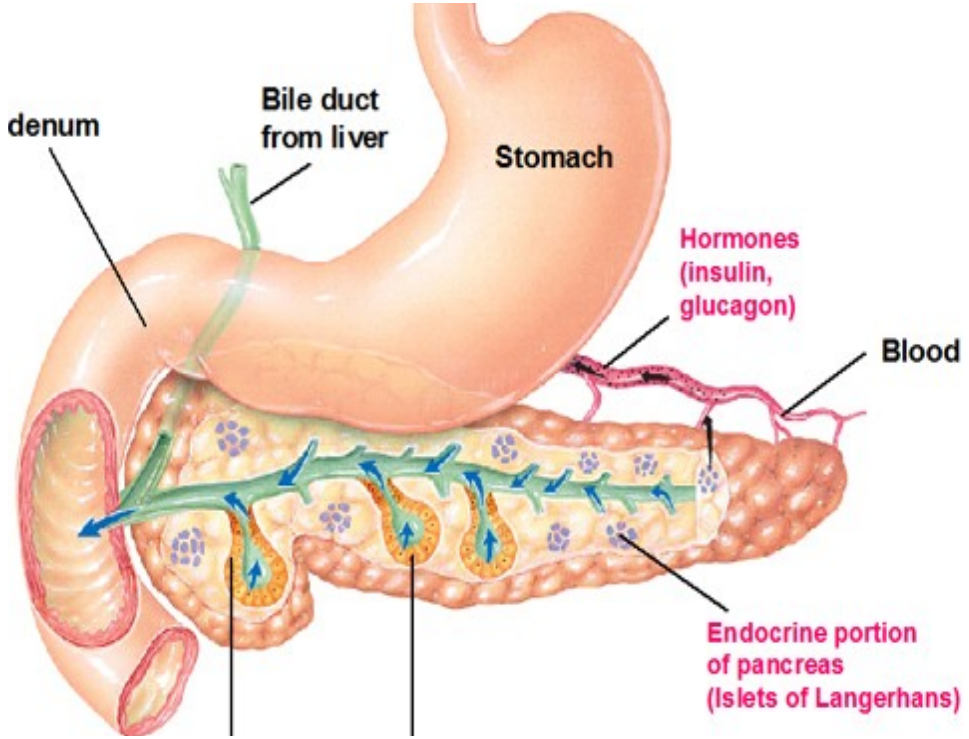
1. Alpha cells Glucagon
2. Beta cells Insulin
3. Delta cells Somatostatin
4. F cells Pancreatic polypeptide (PP).



- Beta cells are centrally located within the islet and constitute 60% of the islet mass.

- Alpha cells (25%) , **D** cells (10%) and **F** cells (5%) cells are located at the

What are the hormones secreted by Pancreas?



- Insulin
- Glucagon
- Somatostatin

- Digestive Enzymes and Bicarbonate

What are the hormones secreted by Pancreas?

Endocrine gland	Hormone	Function
Pancreas	Insulin	Increase uptake of glucose into the cell; promotes glycogenesis; lowers blood sugar levels
	Glucagon	Promotes glycogenolysis; Increases blood sugar levels
	Somatostatin	Mild inhibition of insulin and glucagon preventing fluctuations in blood glucose levels. Decreases gut motility and secretion of digestive juices

Insulin Hormone

(Hormone of feasting not fasting)

- **Site of release:**

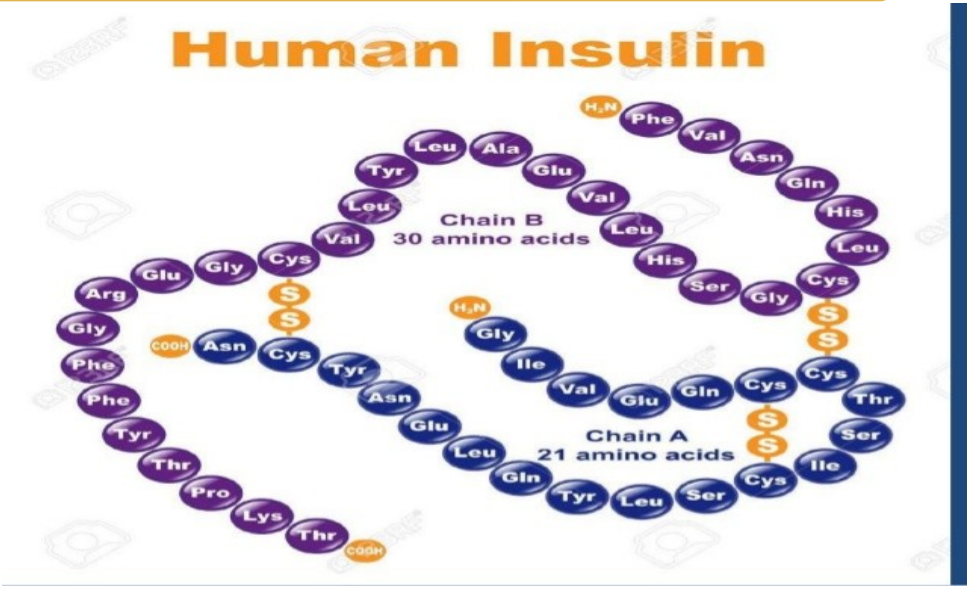
Beta cells of the islets of Langerhans in response to rising levels of blood glucose.

- **Nature:**

Peptide hormone (51 a.a) consisting of two chains linked together by disulfide bridges..

- **Synthesis:**

- It is synthesized as pre-proinsulin, stored in secretory granules as proinsulin & released as mature insulin by exocytosis.
- It circulates free (not bound to plasma proteins).



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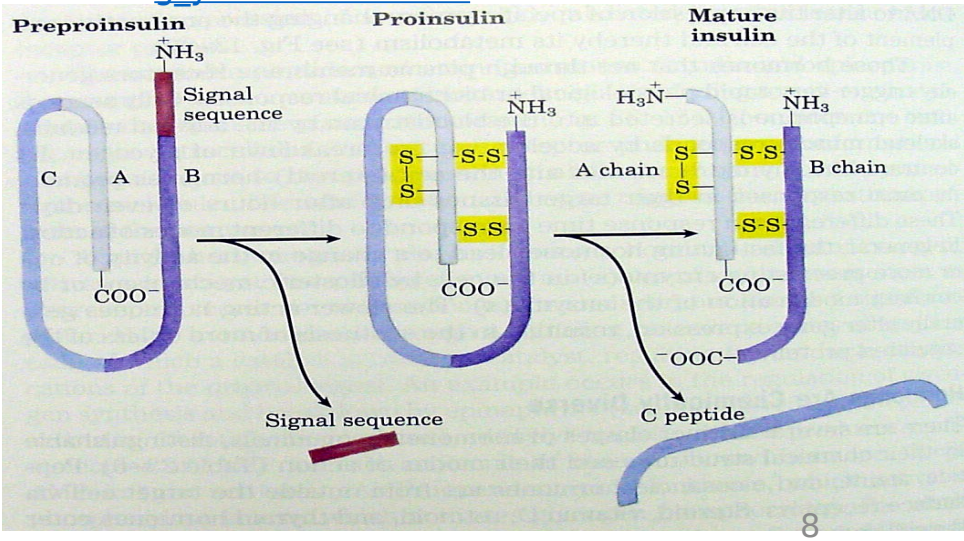
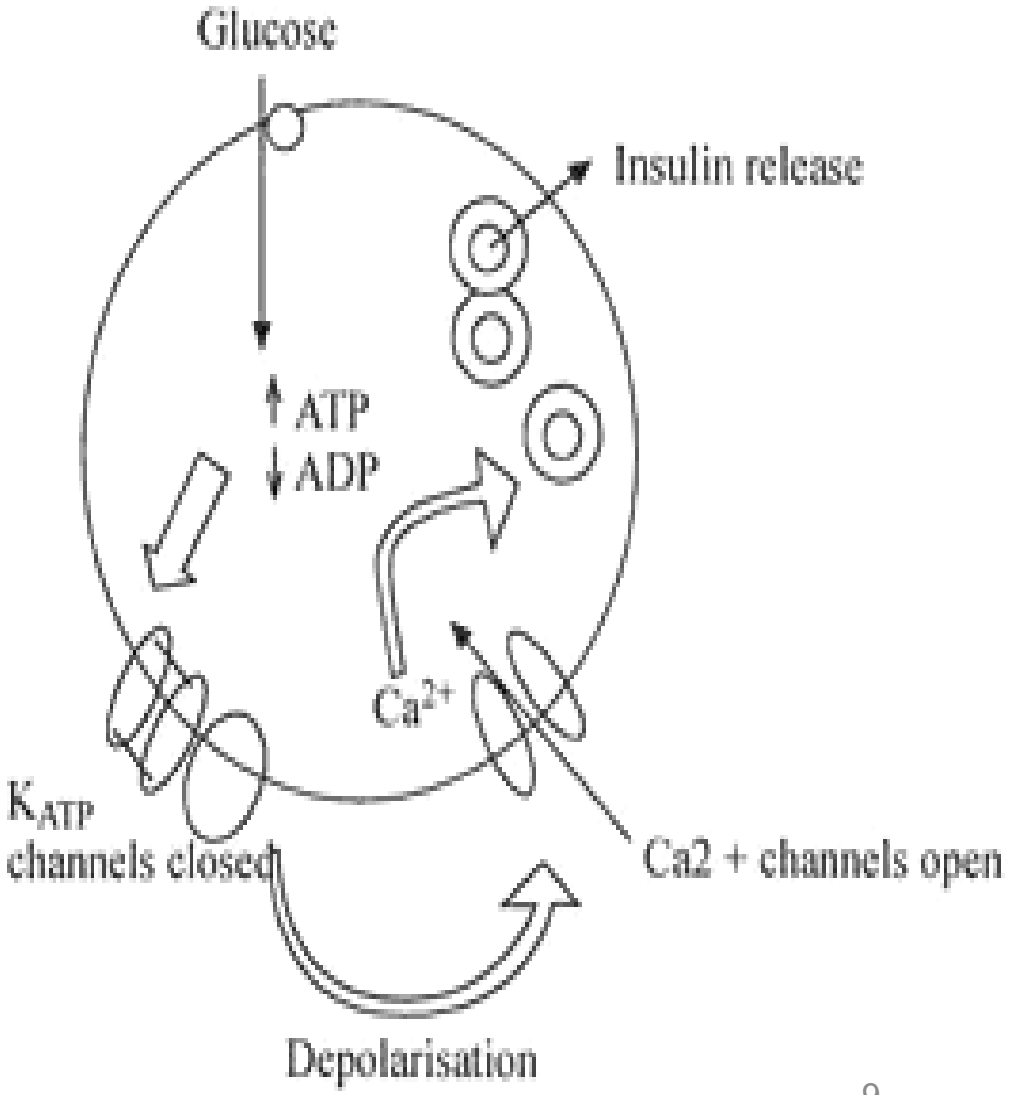
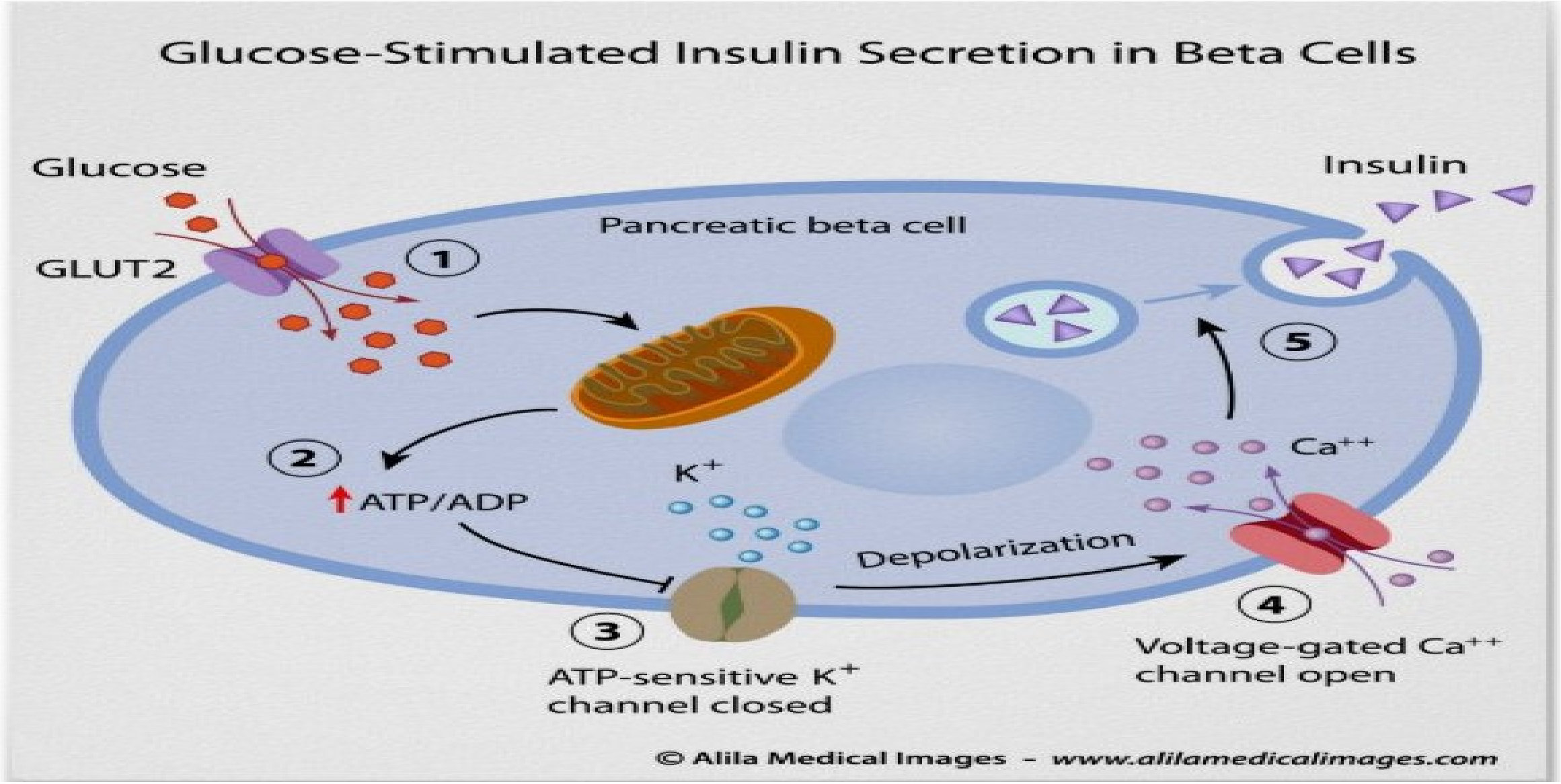


Insulin Hormone

Glucose induced insulin secretion

- Glucose enters the beta cells via **GLUT2** transporter
  - Glucose is metabolized generating ATP
  - ATP closes the **ATP sensitive K+ channels**
    - ↓ K efflux
    - Depolarizes the cell membrane
    - Opening of voltage gated **Ca++ channels** in the beta cell membrane





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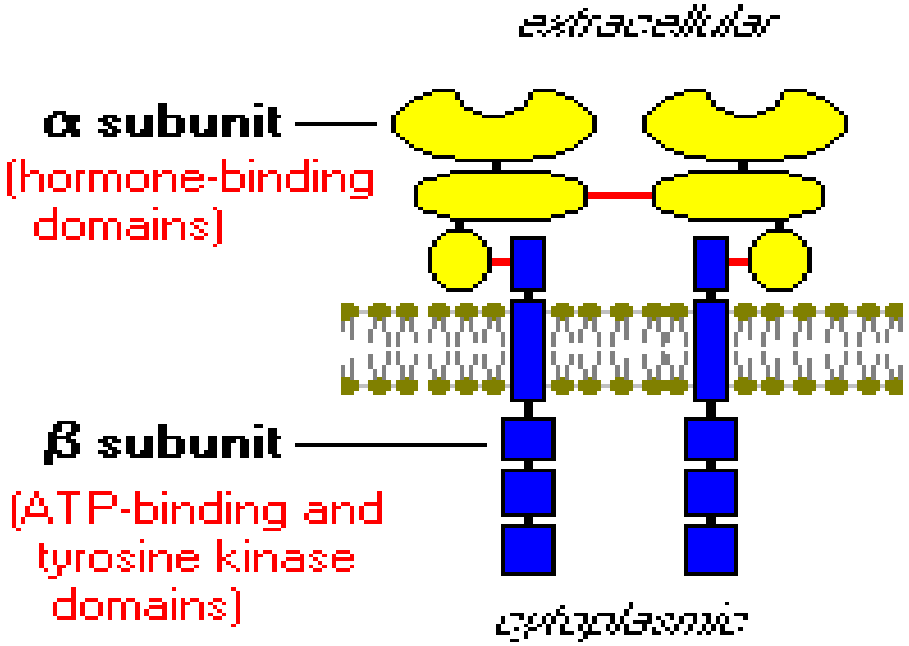
Insulin Hormone

- **Mechanism of action:**

Insulin receptors:

- The insulin receptor is a complex protein made of 2 α subunits & 2 β subunits linked by disulfide bonds.

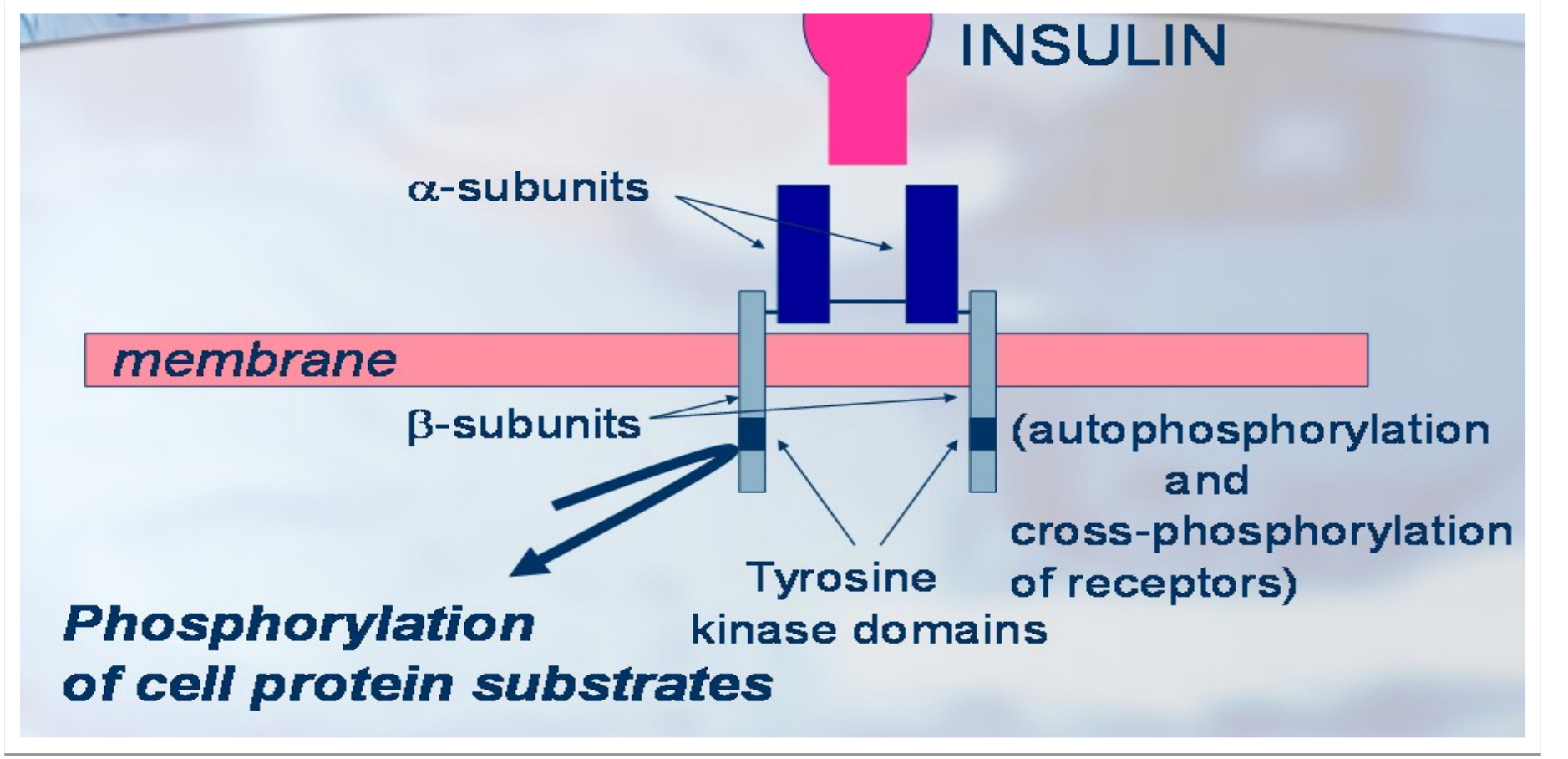


- The ***α subunit*** of insulin receptor is extracellular and bind to insulin while the ***β subunit*** span the membrane & has intracellular part with intrinsic tyrosine kinase activity.*(The insulin receptor functions as a tyrosine kinase).*
- Binding of insulin to ***α*** subunit

→(+) the tyrosine kinase activity of β subunit **(Autophosphorylation of β subunit)**

 Phosphorylation of a number of intracellular proteins (e.g IRS -1 that mediates most of the biological effects of insulin).

INSULIN RECEPTORS

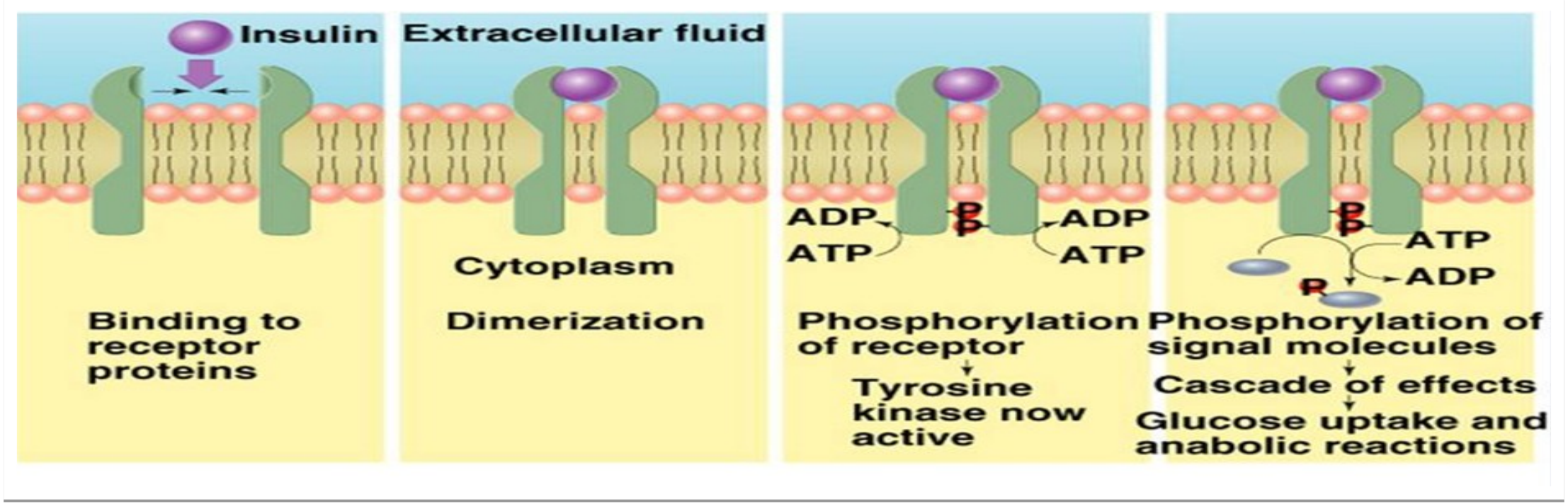


- **The number of insulin receptors are affected by insulin and other hormones, exercise & food e.g**

✓ **↑ insulin (<u>obesity</u> and <u>acromegaly</u>) → ↓ number of receptors = down regulation.**

✓ **↓ insulin (<u>starvation</u>) → ↑ number of receptors = up**

Mechanism of action of insulin hormone



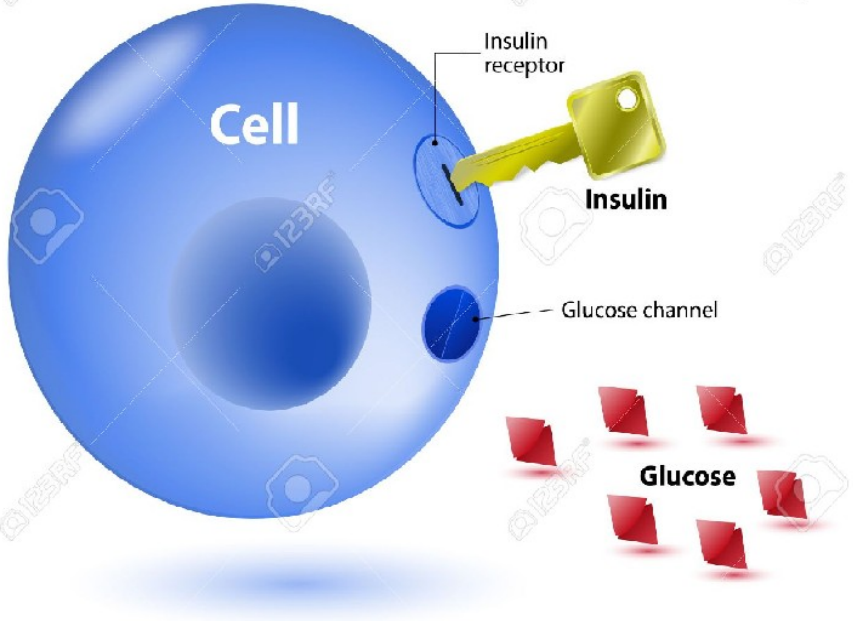
Binding of insulin to the **α** subunits causes the **β** subunits to phosphorylate themselves **(autophosphorylation),** thus activating the catalytic activity of the receptor. The activated receptor then phosphorylates a number of intracellular proteins that mediates the biological effects of insulin.

Insulin Hormone

Physiological actions :

I- On CHO:

- (+) glucose uptake in muscle and liver.
- (+) glycogen synthesis = glycogenesis in muscle &li
  glucose is channeled into storage.
- (+) glycolysis in muscles and adipose tissue.
- (-) glycogenolysis and gluconeogenesis.



Insulin is the only hypoglycemic hormone

By

↑ ↑ **Glucose uptake & utilization by the cells.**

↑ ↑ **Glucose storage as glycogen in liver**

Glucose Transporters

✓ Glucose transport across the body cells occurs by :

1. **Secondary active transport:** (**Na^+** - glucose cotransport) (SGLT1 & SGLT2) in intestine & kidney.
2. **Facilitated diffusion:** glucose transporters (GLUT).

Glucose transporters

✓ They are group of membrane proteins which help transport of glucose across the cell (facilitated diffusion).

✓ There are 7 different glucose transporters, named GLUT 1–7.

Typ	characteristics
GLUT 1	Basal glucose uptake (ercs, muscle cells at resting conditions, brain vessels ..)
GLUT 2	Liver, β cells of pancreas , kidney
GLUT 3	Neurons, placental cells
GLUT 4	Muscle, adipocytes – dependent on insulin
GLUT 5	Transport of fructose, small intestine
GLUT 7	Intracelular transport liver

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Glucose Transporters

Does insulin stimulate glucose uptake in all cells ??

NO

Insulin-dependent and insulin-independent organs & tissues

Insulin-dependent organs	Insulin-independent-organs
• Skeletal muscle (Glut-4)	Brain
• Myocardium (Glut-4)	Red blood cells
• Fat tissue (Glut-4)	Kidney medulla
	Inflammatory & granulation tissues, wounds
	Macrophages

Insulin Hormone

- 80% of glucose transport into cells is **insulin dependent** (using glucose transporter **"GLUT" 4**) which is found mainly in cytoplasm of **resting muscles** & **adipose tissues.**
- Insulin promotes glucose uptake in them by ↑ the number of glucose transporters and promotes their movement from cytoplasm to cell membrane.

Insulin independent glucose transport occurs in:

(via glucose transporters = plasma membrane carriers)

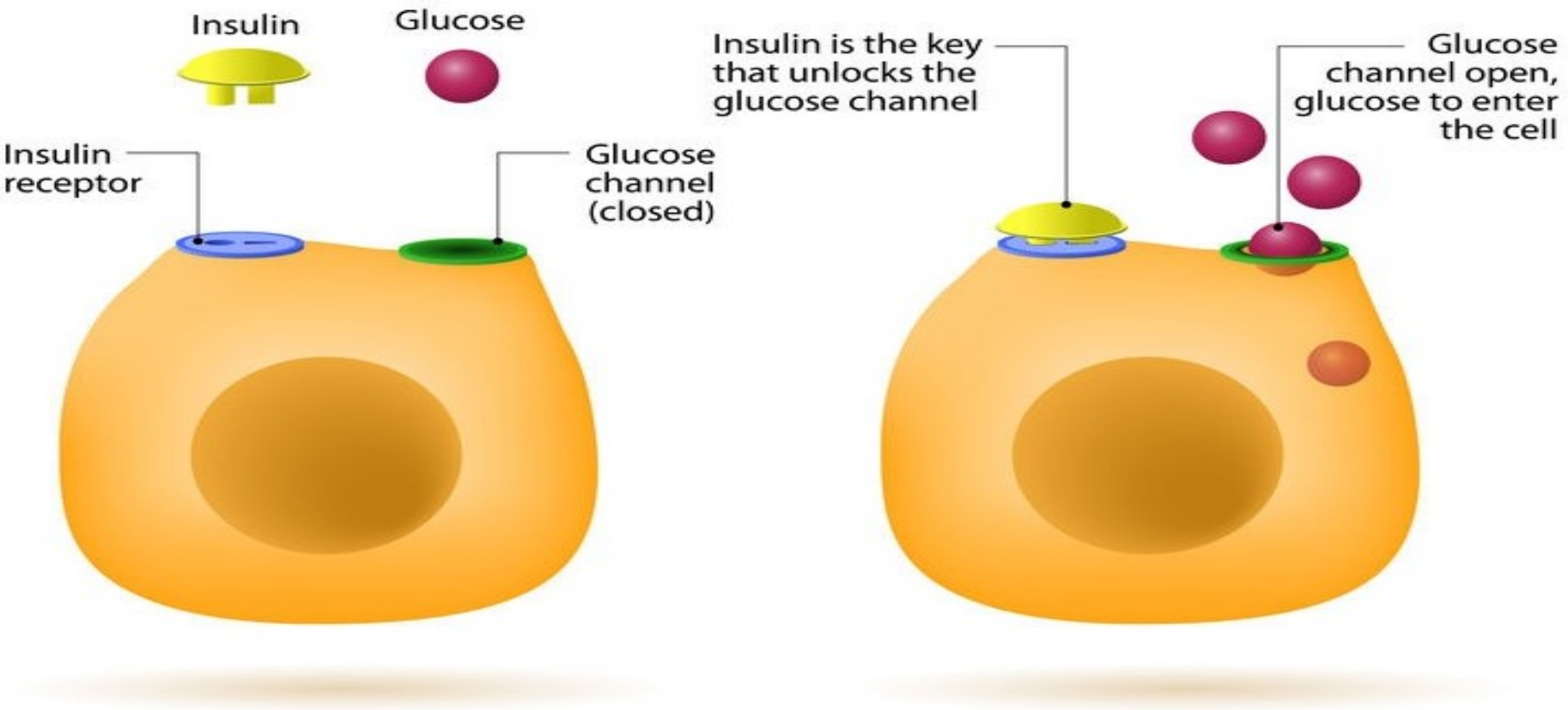
1- Brain (except satiety center) GLUT 1

2- RBCs, gonads, placenta GLUT 1

3-Intestine, kidney, liver & B cells of pancreas GLUT 2

4- Neurons GLUT 3

HOW DOES INSULIN WORK?



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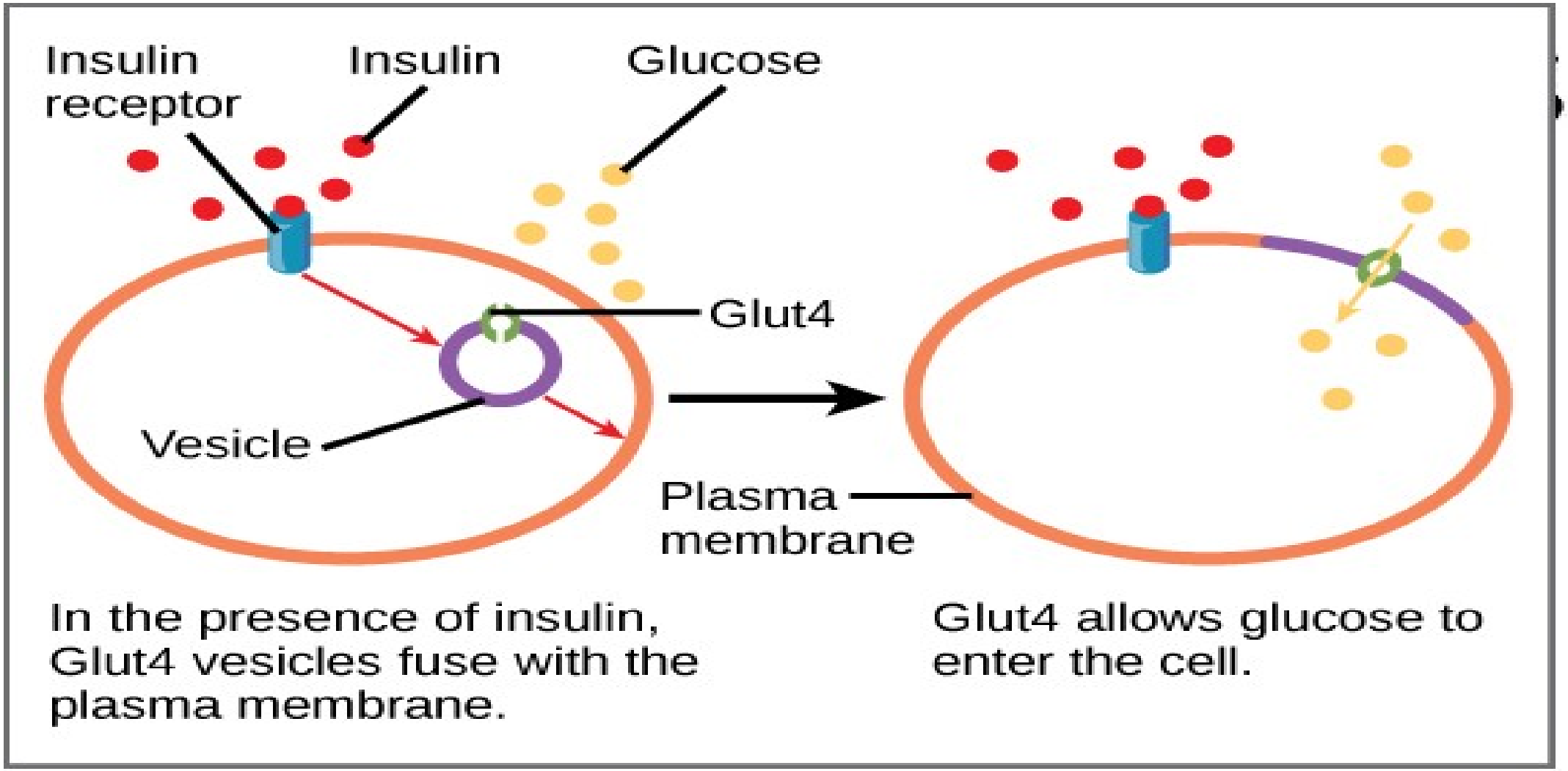
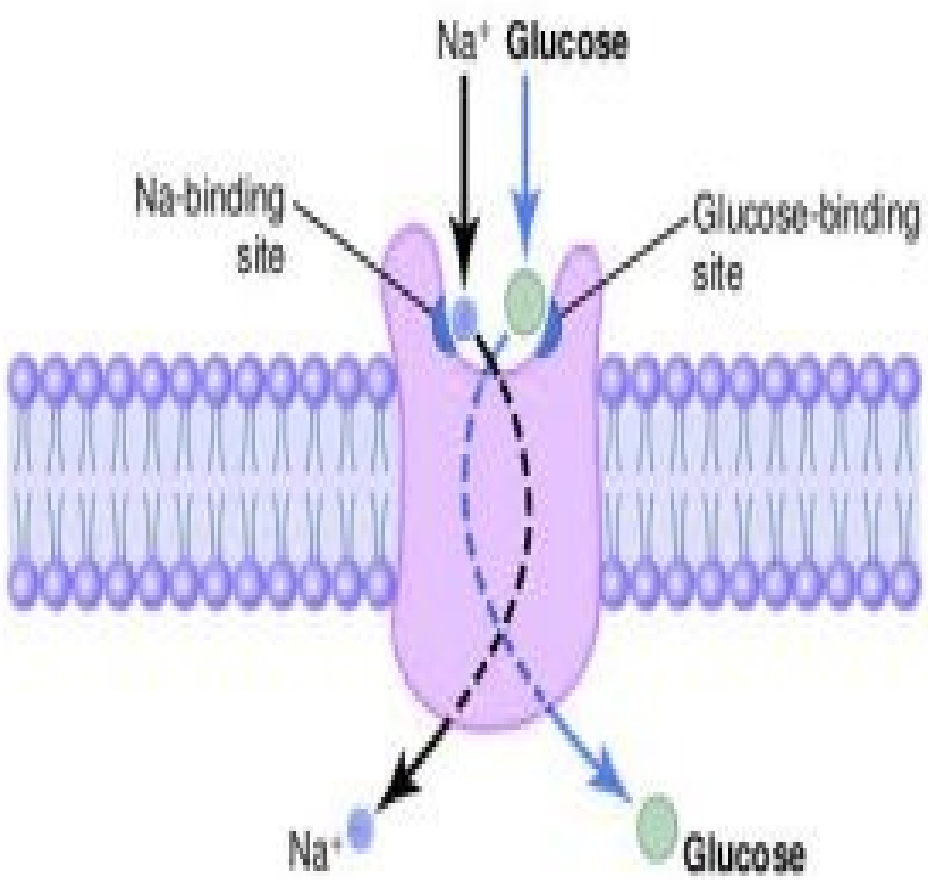
Insulin stimulated glucose uptake via GLUT 4:



Secondary active transport of glucose in renal tubules:



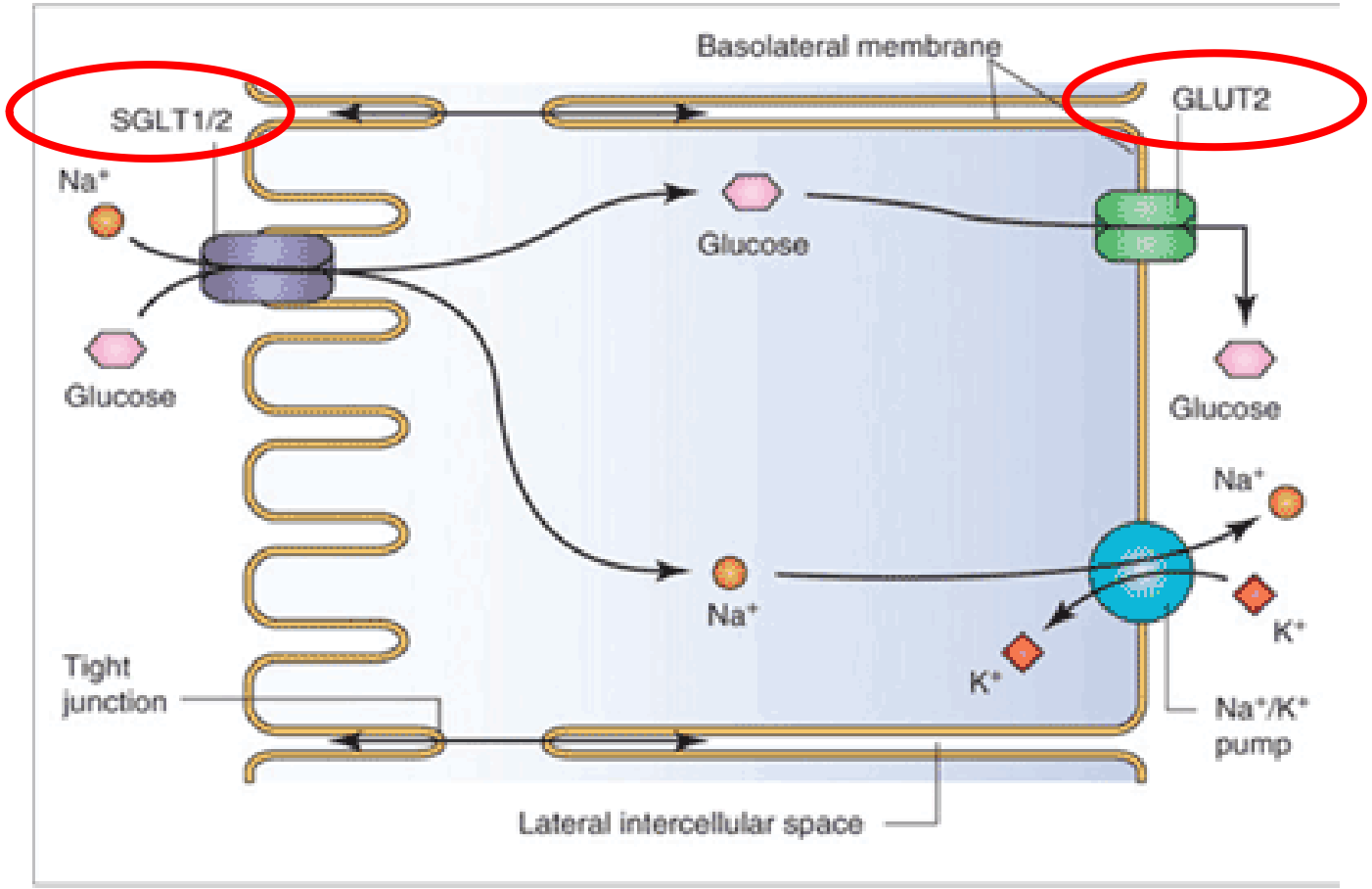


Figure 1. Glucose reabsorption from the glomerular filtrate through a proximal tubule epithelial cell into the blood. Reprinted by permission from Macmillan Publishers Ltd: Kidney Int. *2009;75:1272-1277.*
© 2009 www.nature.com/ki/journal/v75/n12/fig_tab/ki200987f1.html#figure-title.
Source: Reference 7.

Insulin Hormone

II- On FAT:

- (+) fat deposition (lipogenesis) & (-) lipolysis in adipose T. ↓ fatty acids level in blood.
- (-) ketogenesis (ketone bodies formation) in the liver because it ↓ fatty acid degradation providing less acetyl-CoA, the substrate for their formation.

So insulin is a lipogenic hormone.

III- On proteins:

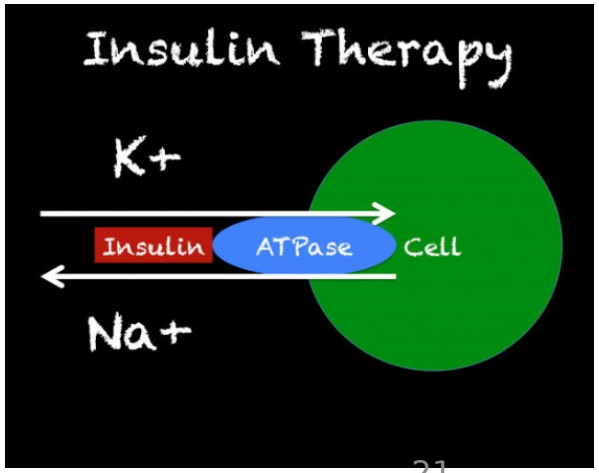
- (+) amino acid uptake into cells, increases protein synthesis ↓ a.a level in blood.
- (-) protein degradation.(+ve nitrogen balance).

So insulin is an anabolic hormone.

IV- On electrolytes:

- Insulin increases K+ uptake into cells, so decreasing blood K+.

(Insulin ++ activity of Na^+- K^+ ATPase).



Insulin Hormone

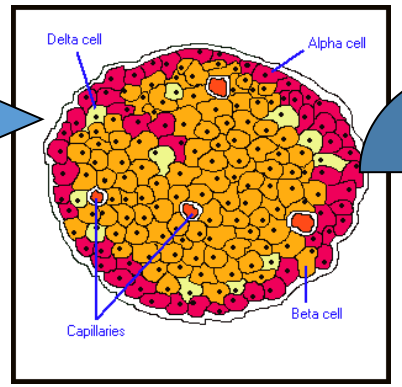
- So insulin is **Hypoglycemic,**

Lipogenic,

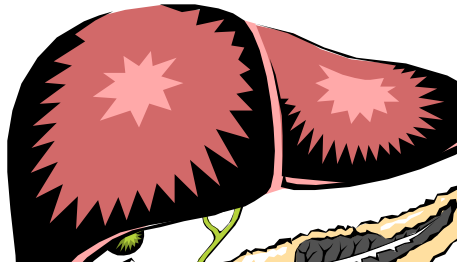
Anabolic.

- Insulin actions can be divided into rapid, intermediate, and delayed actions as follows:

Rapid	Intermediate	Delayed
Seconds	Minutes	Hours
↑ transport of glucose, amino acids, and K^+ into insulin-sensitive cells	- (+) glycolytic enzymes and glycogen synthase - (-) phosphorylase & gluconeogenic enzymes - (+) of protein synthesis	↑ in mRNAs for lipogenic enzymes



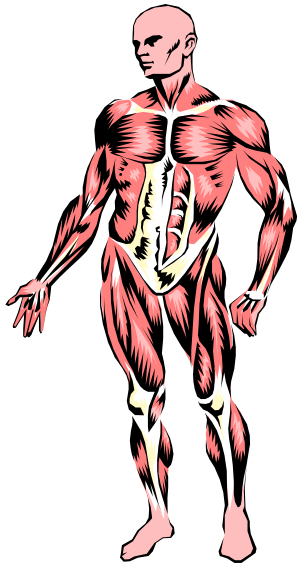
INSULIN



(+) Glycogenesis, glycolysis

- **↓ glycogenolysis**
- **↓ gluconeogenesis**

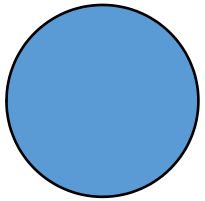
↓ ketone body production

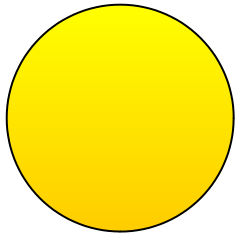


Glucose uptake (Glut4) □ glycogenesis, glycolysis

Amino acid uptake □ protein synthesis

↓ protein breakdown





Lipogenesis (□TG)

↓ lipolysis

Glucose uptake (Glut4) □ glycolysis

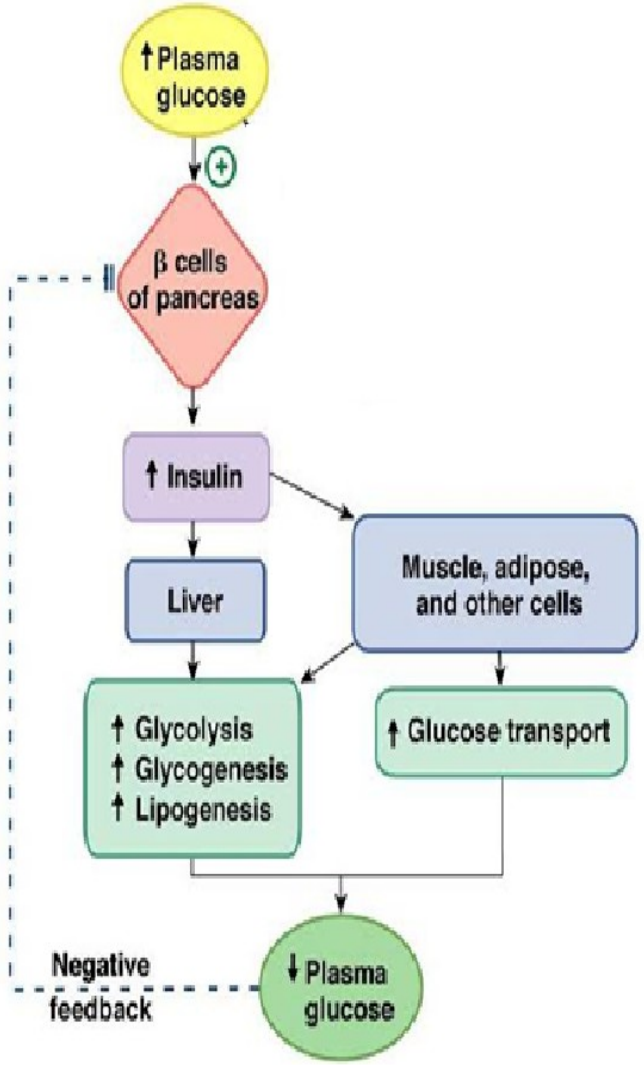
Regulation of insulin secretion

I. Blood glucose concentration:

- The most important factor regulating insulin secretion.
- ↑ blood glucose (+) insulin secretion from the -cells

  ↓ blood glucose.
- ↓ blood glucose (-) insulin secretion.

  ↑ blood glucose **(-ve feedback)**



- Insulin secretion is **biphasic**, an initial burst of insulin (release of preformed insulin) is followed by slow sustained secretion (release of newly formed insulin).

Regulation of insulin secretion

II- Blood amino acid level:

 amino acids (after a protein rich meal) lead to insulin secretion   amino acid entry into the cells (+) protein synthesis.

III- Gastrointestinal hormones:

- GIT hormones released in response to presence of food (GLP-1, GIP , gastrin, secretin & CCK)   insulin secretion.

NB.: Glucose taken by mouth stimulates more insulin release than given intravenous.

IV- Autonomic nerves:

- Parasympathetic (vagal) stimulation in response to presence of food in GIT   insulin. ***(Ach via M4 receptors).***
- Sympathetic stimulation ↓ insulin   blood glucose level to face stressful situations ***(NE via α 2 receptors).***

Regulation of insulin secretion

V- Other hormones:

- **Glucagon** → (+) insulin.
- **Somatostatin** → (-) insulin.
- **Growth hormone** → (+) insulin.

VII- Cyclic AMP:

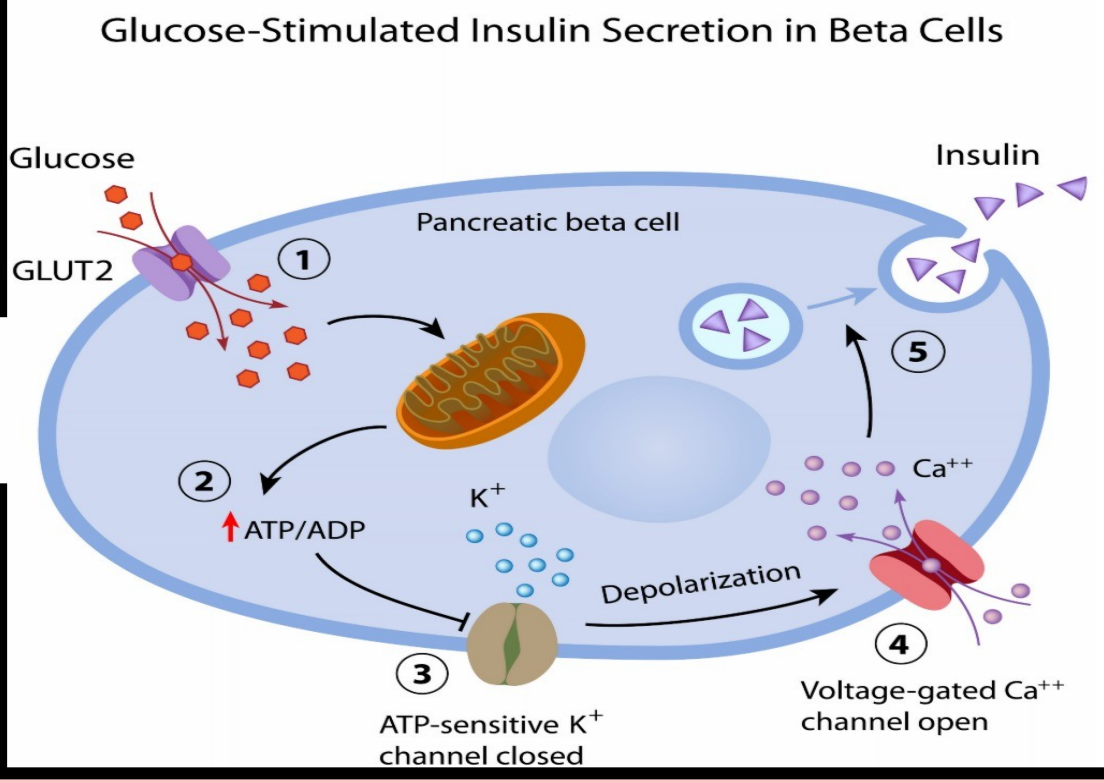
- Stimuli that ↑ cAMP in B cells → (+) insulin as **β adrenergic agonists**, **glucagon** & **theophyline**.

VIII- Ions:

- **K +**and **ca++** are needed for insulin response to glucose.
- K depletion → (-) insulin secretion → glucose intolerance as in ***Conn's disease.***

Regulation of insulin secretion (summary)

Nutrients:
- Glucose
- Amino acids
- Fatty acids



Hormones:
- GIP
- Glucagon
- GH

Neurotransmitters:
- Ach (M4 receptors)

Ions:
- K+
- Ca++

Drugs:
- ↑ CAMP (β-Adrenergic agonists, theophylline,glucagon)
- Sulfonylurea drugs

Regulation of insulin secretion

↑ Insulin Secretion	↓ Insulin Secretion
- ↑ blood glucose - ↑ blood free fatty acids - ↑ blood amino acids. - **Gastrointestinal hormones** (GLP-1, GIP) - Islet hormone (glucagon) - Other hormones (growth hr, cortisol) . - Parasympathetic stimulation; Acetylcholine. - **CAMP** (β-Adrenergic agonists, theophlline).	- ↓ blood glucose (Fasting). - Somatostatin - Sympathetic stimulation (α-adrenergic activity) - Atropine. - β blockers. - Alloxan & Streptozotocin.

Lecture Quiz

Q. Insulin exerts all of the following effects <u>EXCEPT</u>:

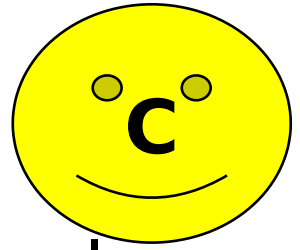
a. Promotion of lipogenesis.

b. Stimulation of glycogen synthesis.

c. Increases transport of glucose into exercising muscle.

d. Increase in glucose transport in adipocytes.

e. Lowers plasma K^+ level.



SUGGESTED TEXTBOOKS

1. **Guyton and Hall Textbook of Medical Physiology.**
   https://www.amazon.com/Guyton-Hall-Textbook-Medical-Physiology/dp/1455770051

2. **Ganong's Review of Medical Physiology, 25e. Chapter 21, pages (315 to 335)**

   https://www.amazon.com/Ganongs-Review-Medical-Physiology-Twenty-Fifth/dp/007182510X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